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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/958,570	10/28/1997	RICHARD J. GREGORY	16930-000921	3556

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EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	32

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/958,570	GREGORY ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24 and 26-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24 and 26-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/28/03 has been entered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-24 and 26-31, 33, 35, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action (Paper #22) and for reasons outlined below.

Applicants traverse this rejection partly by argument and mostly by providing a 37 CFR 1.132 Declaration from Dr. Maneval. Applicants have amended claim 16 to read on a method of treating a tumor (rather than a pathology) using an adenoviral vector

comprising a tumor suppressor gene and applicants and declarant argue that this amendment renders the claims not overly broad.

Applicants' response and the Declaration filed under 37 CFR 1.132 filed 5/28/03 are insufficient to overcome the rejection of claims 16-24 and 26-41 based upon 35 USC 112, 1st paragraph as set forth in the last Office action because: The amended claims, while reduced in scope, are still broad in nature. Indeed, declarant, on p. 4 of the Declaration, notes that over 50% of all human tumors possess defects in p53 or p53 function. Therefore, the claims read on methods of treating a wide range of tumors in any animal and the scope of the invention must be considered broad.

Applicants and declarant argue that the instant invention is enabled by the specification. Applicants and declarant assert that the instant specification provides a description of suitable adenoviral vectors, suitable tumor suppressor genes and promoters, modes and locations of administration, and provides a working example involving use of p53 to inhibit DNA synthesis and suppress growth of a broad range of tumor cell types.

In response, the examiner notes that the specification does not address the art recognized hurdles to successful practicing of gene therapy for treatment of cancer. These hurdles include poor targeting of the vectors to appropriate target cells, unpredictable expression of the transgene, the pre-existence of (or generation of) anti-adenoviral antibodies which limit subsequent uses of the vector, etc. Additionally, Gomez-Navarro et al. (European Journal of Cancer, Vol. 35, No. 6, pp. 867-885, 1999) notes that tumor suppressor mutation compensation gene therapy protocols face many

obstacles to clinical use. These obstacles include the ability of some tumors to show persistent tumorigenicity and proliferation after successful restoration of wild-type genes, a phenomenon referred to as "tumour suppressor resistance" (p. 869) and problems associated with the heterogeneous nature of many human tumors. Specifically, Gomez-Navarro et al. (p. 871) notes that:

Human tumours are remarkably heterogeneous in the patterns of expression of relevant oncogenes. Thus, therapeutic targeting of a single molecular abnormality may have only an inconsequential impact on the clinical management of the disease, considering both the population and individual patients. In addition, several mutated genes produce molecules with transdominant effects, thus necessitating the blocking of their effects and not merely their supplementation with a wild-type version of the gene. Furthermore, because these strategies mostly modulate intracellular responses, nearly every tumour cell might have to be targeted for these approaches to be clinically effective. The current state of development of gene therapy vectors, both viral and non-viral, makes this feat unachievable within non-toxic margins of vector dose. Clearly, breakthrough developments in vector technology are needed for these obstacles to be overcome.

Applicants and declarant indicate that human xenograft models (such as the Hep3B and H69 tumor cell lines implanted in nude mice) are generally accepted as being reasonably predictive of efficacy of anti-cancer treatments in humans. Applicants and declarant assert that their in vivo data demonstrates that an adenoviral vector capable of expressing p53 was effective in reducing the growth of tumors and enhancing the survival times of animals having tumors and that the suicide gene TK was expressed in liver tumors in mice using the methods of the present invention. Applicants therefore assert that the skilled artisan would not have to practice undue experimentation in order to practice the claimed invention.

In response, the examiner again notes that the scientific literature, published after the effective filing date of applicants' invention, teaches that results obtained using

human tumor xenograft models are not predictive of results which could be expected in humans (See Gura, Science, Vol. 278, 1997, pp. 1041-1042, previously cited by the examiner). Specifically, with regard to animal and cell based models for screening of anti-cancer agents, Gura recites:

"The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all", says Alan Oliff, executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania.

Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does. (p. 1041, left column).

With regard to problems associated with human xenograft models, Gura also notes that:

Because the animals can't reject the foreign tissue, the tumors usually grow unchecked, unless stopped by an effective drug. But the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft tumors don't behave like naturally occurring tumors in humans-they don't spread to other tissues, for example. Thus, drugs tested in the xenografts appeared effective but worked poorly in humans. "We had basically discovered compounds that were good mouse drugs rather than good human drugs," says Sausville. (p. 1041, middle column).

Additionally, the examiner notes that adenoviral vectors which appear to show efficacy in animal models and in preliminary human safety trials can behave quite differently and unpredictably when actually used for therapy (Fox, Nature Biotechnology, Vol. 18, 2000, pp. 143-144). Indeed, Fox notes that:

Other factors appear to complicate the clinical use of adenovirus-based gene vectors, according to Wilson and other researchers. For instance, the doses at which there are toxic effects or potentially therapeutic effects may be separated only narrowly, and there may be thresholds where adverse effects abruptly appear-complicating how vectors might be used and perhaps undermining the reliability of results from test

animals. Moreover, such viruses can sometimes provoke or otherwise disrupt cytokine-determined inflammatory responses, according to Linda Gooding of Emory University (Atlanta, GA), one of several experts on a NIH-FDA working group that is reviewing adenovirus-related adverse effects.

Equally if not more problematic for would-be gene-therapy procedures, these vectors are not so reliable in delivering genes to where they are targeted. After the adenovirus vector was applied through a catheter onto the liver of Gelsinger and others in the trial, it spread widely through other organs and also, at least early on, into immune system cells, based on the post mortem analysis of his tissues-distributing quite differently from how it behaved during animal experiments, according to Wilson.

Therefore, given the unpredictability in attempting to extrapolate results obtained in animal models to results which would be expected in humans and given the absence of an art recognized correlation between the results obtained in human xenograft models and the results which would be expected by the skilled artisan to be observed in humans, the results presented by applicants would not be considered by the skilled artisan to be predictive of results which would be obtained in humans.

Applicants and declarant cite several recent articles detailing use of an adenoviral vector in clinical trials (Phase I) wherein said vector expresses p53 and is deleted in pIX. Applicants and declarant indicate that the articles demonstrate expression of p53 in target tissues by an adenoviral vector deleted in pIX, thus demonstrating the operability of the claimed invention.

In response, the examiner notes that the specific adenoviral vector used in the articles (rAd-p53 SCH 58500) is not disclosed in the instant application and to the extent that the results obtained in the studies are dependent upon the characteristics of this specific vector, said results cannot be used to provide evidence of the enabling nature of the instant specification. Also, it is noted that some of the studies involve use of

adenoviral vectors and specific chemotherapy treatments which again are not taught in the instant specification. Also, it is unclear what effects are due to the vector and what effects are due to the chemotherapy agents, possibly there may be a synergistic effect, etc. The dosages of adenoviral vectors recited in some of the articles appear to be higher than what is disclosed in the instant specification. For example, Wen et al. teaches use of 7.5×10^{13} particles on each of five consecutive days while the instant application teaches that dosages may be between 10^{8} to about 10^{13} infectious units. The dosage used by Wen et al. is not taught or suggested by applicants' disclosure. Also, none of the articles actually demonstrates successful treatment of patients suffering from cancers resulting from defective tumor suppressor genes. All of the articles use very cautious language with regard to the results obtained in the studies and argue for further research and investigation before adenoviral vectors can be actually used in treatment of patients with cancers. It seems curious that while applicants and declarant assert that gene therapy for cancer was enabled at the time of applicants invention, highly skilled researchers in the field (Wen et al., Kuball et al. and Buller et al., all cited by applicants) almost a decade later have yet to actually reduce to practice treatment of patients suffering from cancers.

Applicants and declarant indicate that since the skilled artisan in the gene therapy art is exceptionally highly skilled (applicants cite a printout of a summary of RAC approved Human Gene Transfer Protocols and cite qualifications of numerous researchers in the gene therapy field), said skilled artisan would have been able to practice gene therapy given applicants' disclosure.

In response, the examiner notes that indeed, practitioners in the gene therapy art are exceptionally highly trained and possess many academic credentials. However, when one considers that those of skill in the art at the time of the invention had yet to reduce to practice a single unambiguous example of successful gene therapy (W French Anderson notes that as of 1998, no gene therapy protocol had been demonstrated to be successful), it can be considered that the **relative skill of the artisans in the gene therapy art was (is) very low**. If no one in the gene therapy field can get the procedure to work, how can the level of skill in gene therapy be high? Practitioners in the gene therapy field may have many advanced academic degrees, but if they cannot reduce to practice gene therapy, their level of skill **in the gene therapy field is low**.

Applicants and declarant assert that the "relevant art" supports the therapeutic efficacy of gene therapy and applicants cite several U.S. patents (only one of which has an effective filing date earlier than applicants' invention) which claim gene therapy methods of treating cancer in mammals comprising administering sequences encoding wild type p53 to subjects. Applicants and declarant assert that given the relevant art demonstrating efficacy of p53 gene therapy and the teachings of the instant disclosure, the skilled artisan would only need to have practiced routine experimentation in order to reduce to practice the claimed invention.

In response, it is noted that references published (or with an effective filing date) after the filing date of the instant invention cannot be used to provide evidence of enablement at the time the invention was made. Also, the examiner notes that a

handful of patents issued over the past decade can hardly be considered the relevant art concerning enablement of gene therapy. A more relevant assessment of the gene therapy art was made by the foremost gene therapy practitioner, (W. French Anderson), who notes that as late as 1998, no successful gene therapy protocol had been unambiguously demonstrated (Anderson, Nature, Vol. 392, 1998, previously cited by the examiner). With regard to the one U.S. patent (5,532,220) with a filing date prior to applicants' invention, said patent involves use of a retroviral vector to transfer a p53 gene to target cells. It is noted that clinical retroviral based gene therapy trials have been suspended in the U.S. because of the adverse effects (development of a leukemia like disease in patients) resulting from infection by the recombinant retroviral vector (Marshall, Science, Vol. 299, 2003, p. 320). Also, it is noted that issuance of claims reading on similar subject matter in another application does not entitle applicants to a patent. Although an examiner's action in another case may be inconsistent with the instant application, each case must stand on it's own merits (*In re Giolito*, 188 USPQ 645).

Finally, applicants indicate that the issued U.S. patents on gene therapy adhere to a standard set by the Federal Circuit when addressing pharmaceutical inventions and indicate that the instant application be judged by the same standards.

In response, the examiner notes that the quotation form the Federal Circuit cited by applicants appears to deal with the **utility** of pharmaceutical inventions. This is misplaced here because a utility rejection (under 35 USC 101) has not been made in the prosecution of this application.

For the reasons cited above and for reasons of record the claims stand rejected.

Claims 32, 34, 36-37, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining expression of a tumor suppressor gene product or suicide gene product *in vitro*, does not reasonably provide enablement for said method practiced *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The grounds of rejection here are identical to those in the above enablement rejection and will not be repeated.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-24 and 26-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-24 of copending Application No. 09/860,286 (Publication US 2003/0091534). Although the

conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite a method for treating a pathology in an animal or mammal (or inhibiting proliferation of a tumor), said method comprising administering to target cells an adenoviral vector capable of expressing a protein having tumor suppressive function or a suicide protein. The instant claims differ from those in the '286 application in that instant claim 16 is limited to a method for treating a tumor in an animal; however, claim 16 in the '286 application recites a method for treating a pathology but also recites administration of a gene with a tumor suppressive function and therefore said method is to be used to treat a tumor in an animal. The instant claims differ from those in the '286 application in that instant claim 19 recites administering a gene encoding a protein with tumor suppressive function while claim 19 in the '286 patent recites administering a gene encoding a foreign protein; however, subsequent claims dependent upon claim 19 in the '286 application recite that the foreign gene encodes a tumor suppressive agent. With regard to the instant claims reading on a method for obtaining expression of a tumor suppressor or suicide gene in a cell, it is noted that the claims in the '286 application (see claims 17, 21 in the '286 application) also read on a method of expressing a tumor suppressor or suicide gene in a cell in the context of treating a pathology or tumor in an animal. The claims in the '286 application would therefore anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be submitted directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
July 22, 2003

DAVID GUZO
PRIMARY EXAMINER